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09/547,215	04/11/2000	Andrew V. Schally	SHAL3.031	4694

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SELITTO, BEHR & KIM, P.C.
P.O. BOX 1477
100 PLAINFIELD AVENUE
Edison, NJ 08818

EXAMINER	
YU, MISOOK	
ART UNIT	PAPER NUMBER
1642	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/547,215	Applicant(s) SCHALLY ET AL.	
	Examiner Misook Yu	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). *9,10,11* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of applicant's interview summary for the telephonic interview occurred on June 10, 2002) in Paper No. 12 is acknowledged.

Priority

Applicant's amendment claiming priority to US nonprovisional application 09/199,381 in Paper No. 12 is acknowledged and has been entered.

Election/Restrictions

The restriction requirement set forth in Paper No. 7 is withdrawn because applicant pointed out during the telephonic interview on June 10, 2002 that the instant application is a division of an US nonprovisional application 09/199,381 and there was no restriction requirement for the different compounds listed in claims 9-11.

Applicant's election without traverse of species peptides 1 and 3 listed in the instant claims 12-17 in Paper No. 8 is acknowledged.

Claims 9-17 are pending and examined on merits as they are drawn to the elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9, 10, and 11 recite the limitation "an effective amount" but it is not clear what the metes and bounds for "an effective amount". Is it certain a quantitative range? For example, 20 microgram a day for 20 days? The only dosage mentioned in the specification is 20 microgram a day for several different days at pages 34-38.

Claims 9, 12, and 13 are indefinite because claim 9 recites the phrase "suppressing excessive levels of GH in a patient in need of same". It is unclear what is

meant by "suppressing excessive levels of GH in a patient in need of same" or what parameters of "suppressing excessive levels of GH in a patient in need of same" are being claimed for patent protection. Is the claimed invention in claims 9, 12, and 13 a treatment method for certain diseases? If so, what are the specific diseases that could be treated using the claimed invention of claims 9, 12, and 13? Who is a patient with excessive levels of GH in need of suppressing level of GH?

For this office action, this examiner will assume that "method of suppressing excessive levels of GH in a patient in need of same" is a method of suppressing excessive levels of GH in a patient suffering from acromegaly, since the instant specification at page 19 line 22 gives an example of a condition caused by excessive level growth hormone as "acromegaly". However, this treatment does not relieve applicant the burden of responding to this rejection.

Claim 11 recites the limitation "said patient" in line 3. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 12, and 13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 9, 12, and 13 are drawn to method of suppressing excessive levels of GH in a patient by administering ***an effective amount*** of a compound, peptide 1, 3, or any of the peptides identified in claim 9 to said patient. The specification discusses tumor treatment in detail, but it is not clear what disease(s) is treated by suppressing excessive levels of GH in a patient in need of same. The specification at page 19 line 22 gives an example of a condition caused by excessive level of growth hormone as "acromegaly" but the specification

does not give any guidance or examples of how to accomplish the purpose stated in the preamble of claim 9. Applicant's invention in the instant claims 9, 12, and 13 is administering an effective amount of the compounds listed in claims 9, 12, and 13 to a patient for the purpose stated in preamble of claim 9.

The specification shows in Table II and III (page 32): 1) inhibition of GH release in vitro rat pituitary culture cells by peptides 1 and 3; 2) peptides 1 and 3 in vitro have higher receptor binding activity than the control. The specification in Table IV at page 33 shows serum GH level is low when normal mice are given peptides 1 and 3. However, the data in Table II-IV do not establish to whom peptides 1 or 3 should be given in order to accomplish the purpose stated in the preamble of claim 9. Further, the data in Table II-IV do not establish ***an effective amount*** of peptides 1 and 3 in order to accomplish the purpose stated in preamble of claim 9. The specification fails to teach that: (1) what is ***an effective amount*** of peptide 1 or 3 to accomplish the purpose stated in preamble of claim 9; (2) ***which patient is "in need of same"*** as recited in claim 9. If the method using the elected peptide 1 or 3 is directed at lowering excessive serum GH level in a patient suffering acromegaly, then what is the effective amount of peptide 1 or 3? How (what routes?, oral, intravenous, or intramuscular?) should be administered in order to accomplish the purpose stated in the preamble? How often should a compound administered in order to accomplish the purpose stated in the preamble?

Without exemplification for accomplishing the purpose stated in preamble of claim 9 using the claimed invention in the specification, the lack of sufficient guidance concerning the issues raised above, it is concluded that undue experimentation would be required for one skilled in the art to use the invention as claimed.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for peptide 1 and 3, does not reasonably provide enablement for any other compound in claim 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

use the invention commensurate in scope with these claims. Claim 10 is drawn to method of treating cancer patient carrying receptors for IGF-I or -II by administering an effective amount of a compound, peptide 1, 3, or any of the compound listed in claim 10 to said patient.

The specification in Fig. 1-5, Table V (page 35), Table VI (page 36), Tables VII and VIII (page 37), and Table IX (page 38) teaches that tumor volume is lower in vivo tumor model that received daily 20 micrograms subcutaneous injections (at pages 34-38) of peptide 1 or 3 for certain days, compared to control.

One cannot extrapolate the teaching of the specification to the claim because it is well known in the art that even slight modifications in a peptide or protein structure can have significant and unpredictable effects on biological activity as discussed in prior office action in Paper No.7 at page 2, third paragraph. Seto et (1990, Biochem. Biophys. Res. Commun 167, 360-336) teaches at Table 1 and abstract that analogs #5, 10, 19, and 21 are identical species of the compounds in instant claim 9-11 and further teach that substitution or modification at any position of the peptide (SEQ ID NO:1 of the instant application) is well known in the art before the effective filing date of the instant application. Seto et (1990, Biochem. Biophys. Res. Commun 167, 360-336) teach that the different modification or substitutions of SEQ ID NO:1 of the instant application (see page 361, 2nd and 3rd lines of Materials and Methods section) is to search for the best peptide analog to inhibit growth hormone secretion stimulated by human growth hormone-releasing factor (note analog #21 at Table 1). Seto et al also teach that slight modification of SEQ ID NO:1 of the instant application turns the modified peptide into an potent antagonist to the original peptide (see #21 analog of Table 1 and the last sentence of the abstract). In addition, Bowie et al (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out biological activity and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is

known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid (including conservative substitutions) in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or even with conservative glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein.

Further, one cannot extrapolate the teaching of the specification to the claim because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to

overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed peptide would be useful for treating cancer. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

The specification does not teach the specific structures responsible for anti-tumor activity, nor provide guidance as to what changes in the structure can be made retaining anti-tumor activity. The specification provides insufficient guidance to one skilled in the art to predict the efficacy of the claimed invention with a reasonable expectation of success for cancer treatment. Considering the broad scope of the claims, and the limited teachings of the specification, it is concluded that undue experimentation would be required to enable the full scope of the claims.

Claims 11, 16, and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 11, 16, and 17 are drawn to method of inhibiting IGF-II protein and IGF-II mRNA levels in cancer cells by administering the GH-RH antagonists listed in claim 11, 16, and 17 to a patient. The

specification in the paragraph bridging page 21 and 22 says that the antagonistic analogs of GH-RH listed in lines 19-21 of page 21 of the instant application inhibited IGF-II expression in vivo tumors but the specification does not teach if any of the products listed in claims 11, 16, or 17 could inhibit IGH levels in tumors.

One cannot extrapolate the teaching of the specification to the claims because it is well known in the art that even slight modifications in a peptide or protein structure can have significant and unpredictable effects on biological activity as discussed supra and in prior office action in Paper No.7 at page 2, third paragraph.

The specification provides insufficient guidance, and provides no working examples which would provide guidance to one skilled in the art to use the claimed invention for the purpose stated in preamble of the claims without undue experimentation, and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed invention with a reasonable expectation of success. Considering lack of examples and the limited teachings of the specification, and unpredictability in the art, it is concluded that undue experimentation would be required to enable the full scope of the claims.

Claims 11, 16, and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 11, 16, and 17 are drawn to method of inhibiting IGF-II protein and IGF-II mRNA levels in cancer cells by administering GH-RH antagonists listed in claims 11, 16, and 17 to a patient. Although the specification describes that the products listed in lines 19-21 of page 21 of the instant application inhibited IGF-II expression in vivo tumors but the specification does not describe a method of inhibiting IGF-II using the products listed in claims 11, 16, or 17.

For the purpose of compact prosecution, this examiner will search the prior art to the extent the specification is enabled for the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 9-12 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 95/1607 (22 June 1995).

(0-2607) Claims 9-12 are drawn to method of treatment of conditions caused by excessive growth hormone by administering hGH-RH antagonists listed in claims 9-13.

WO 95/1607 (22 June 1995) teaches: *1)* synthetic analogues of hGH-RH(1-29)NH_2 at pages 5 and 6 (note the highlighted products of WO 95/1607 are identical to those of the instantly claimed products in claims 9-11); *2)* how to make the synthetic analogues and pharmaceutical compositions comprising the synthetic analogues of hGH-RH(1-29)NH_2 in pages 14-20 along; *3)* use of the synthetic analogues in therapeutic treatments for condition (for example, acromegaly and others) caused by "excessive level of GH" recited in claim 9, treatment of cancer recited in claim 10, and inhibition of IGF-I or II recited in claim 11. Note pages 21 and 22 for therapeutic uses of the products.

Thus, WO 95/1607 (22 June 1995) anticipates claims 9-12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO WO 95/16707 (cited above, 22 June 1995) and Sato et al (cited above).

Claims 9-11 are drawn to method of suppressing GH level (claim 9), treating cancer (claim 10), and inhibiting IGF-II (claim 11) using any one of about 85 million possible compounds listed in claims 9-11. WO 95/16707 discloses therapeutic uses of the compounds listed in claims 9-11 as set forth above and both Sato et al (see Table 1, Figure 1) and WO ~~94/09820~~ 95/16707 (see pages 5 and 6) teaches synthetic analogs of human growth hormone releasing factor (hGH-RH) with antagonistic activity to hGH-RH. Sato et al (see Table 1, Figure 1) further teaches several compounds actually have antagonistic potency and gives guidance at page 363 what changes in each of the amino acid could be made to achieve antagonistic activity. Both Sato et al (see Table 1, Figure 1) and WO ~~94/09820~~ 95/16707 (see pages 5and 6) further teaches the possible substitutions and modifications at each of the positions in the instant SEQ ID NO:1, hGH-RH (1-29) NH_2 in order for the synthetic analogs of hGH-RH to act antagonists. WO ~~94/09820~~ 95/16707 further teaches at page 1 that Growth Hormone (GH) is implicated in several serious human diseases and these diseases could be treated by administering a GH-RH (last paragraph of page 1) and teaches further medical applications in page 9, third paragraph. WO ~~94/09820~~ 95/16707 specifically teaches at pages 21 and 22 that hGH-RH antagonists can be used in suppressing GH level (instant claim 9), treating cancer (instant claim 10), and inhibiting IGF-II (instant claim 11). Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to test if the hGH-RH analogs taught by both Sato et al (see Table 1, Figure 1)

and WO 94/09820 (see pages 5and 6) have efficacy in suppressing GH level, treating cancer, and inhibiting IGF-II.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Misook Yu whose telephone number is 703-308-2454. The examiner can normally be reached on 8 A.M. to 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Misook Yu, Ph.D.
July 11, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600